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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,722	11/19/2001	Avi J. Ashkenazi	P2730P1C63	1427

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,722	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124,129-131 and 135-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124,129-131 and 135-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments filed on 25 August 2005 and 30 June 2006 have been entered.

Status of Application, Amendments and/or Claims

The Appeal Brief of 11 November 2005 has been entered. Claims 1-123, 125-128 and 132-134 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 124, 129-131 and 135-145 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

Continuity

The objection to the Application for not complying with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), is *withdrawn*. The provisional application contains references to SEQ ID NO: 350. Therefore, the filing date of 16 June 1998 is considered as the priority date.

Written Description

The rejection of Claims 119-123 under 35 U.S.C. § 112, first paragraph- written description, as set forth in the previous Office Action (1 October 2004) is *withdrawn* after further consideration by the examiner. Claims 119-123 have been cancelled by Applicants. Remaining claims do not recite variants of the nucleic acid sequence of SEQ ID NO: 350.

Maintained/New Objects and Rejections

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 124, 129-131 and 135-145 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. The basis for this rejection is set forth in the Advisory Action of 27 April 2005 and at pp. 4-8 of the previous Office Action (1 October 2004).

Specifically, Claims 124, 129-131 and 135-145 are directed to an isolated nucleic acid sequence comprising SEQ ID NO: 350, as well as vectors and host cells comprising.

Applicant's arguments in the response submitted 30 June 2006 and the Brief filed 14 November 2005, as they pertain to the rejections, have been fully considered but are not deemed to be persuasive for the following reasons.

To summarize, for utility of the claimed PRO1153 nucleic acids, Applicant relies on the gene amplification assay for the gene encoding a PRO1153 polypeptide. Applicants argue that Example 170 of the Specification discloses that the PRO1153 gene is significantly amplified in

lung adenocarcinomas and squamous cell carcinomas as compared to normal, non-cancerous human tissue controls (blood). Applicants assert that the PRO1153 gene is useful as a diagnostic marker and a therapeutic target for treatment of tumors. It is the examiner's position that the present specification fails to disclose the physiological significance of the PRO1153 gene or polypeptide, or what the correlation between PRO1153 mRNA and PRO1153 polypeptide expression is, or the significance of any such correlation in lung adenocarcinomas and squamous cell carcinomas. A specific benefit does not exist in currently available form because the skilled artisan would not know if the expression of the PRO1153 polypeptide would be upregulated, down-regulated, or unchanged in cancer. Therefore, Applicant's assertion of the overamplification of the PRO1153 gene does not impute a specific and substantial utility to the PRO1153 nucleic acids.

Applicants assert (Brief, page 11) that it was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Applicant states that Example 170 of the specification discloses that the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8. Applicant explains that a ΔCt value of at least 1.0 was observed for PRO1153 in at least two of the tumors listed in Table 8. Applicant argues that PRO1153 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$ fold amplification or 2.16 fold or 2.85 fold amplification in lung tumors. Applicants submit that the specification has not only disclosed that the DNA copy number for the gene encoding PRO1153 is increased in lung tumors, but has also quantified the degree of gene amplification observed in each of these lung tumors. At p. 4 and 10 of the Brief, and p. 2 of the 30 June 2006 Response, Applicant cites the Declaration of Dr.

Audrey Goddard and contends that absence any evidence to the contrary, the 2.16 to 2.85-fold amplification disclosed for the PRO1153 gene is significant. Applicant states that a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified.

Applicant's arguments have been fully considered but are not found to be persuasive. In the instant case, the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue (lung and squamous). However, there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are also increased in these cancers. Further research needs to be done to determine whether the small increase in PRO1153 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. It is not known whether PRO1153 is expressed in corresponding normal tissues, and what the relative levels of expression are. For example, the gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather than from a matched tissue sample (i.e., healthy lung and squamous), while the literature shows that matched tissue samples are the standard (Pennica et al.; cited in the Office Action of 11 November 2004). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen; cited in the Office Action of 11 November 2004). Therefore, it is not clear that the reported amplification is significant. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1153 is amplified in a variety of samples and invites the artisan to determine the significance of this increase. It remains that, as evidenced by

Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (see *Brenner v. Manson*, (1966, 383 U.S. 519, 148 USPQ 689)).

Applicants refer to the Declaration of Dr. Goddard, submitted with the response (filed 30 June 2006. The Goddard declaration under 37 CFR § 1.132, filed 25 August 2005, has been considered and is deemed insufficient to overcome the rejection of Claims 124, 129-131 and 135-145 based upon 25 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. The Examiner notes that the Goddard declaration is not consistent with the Remarks submitted 30 June 2006 or the Brief submitted 14 November 2005. The Declaration discusses the value of quantitative PCR. However, it does not discuss the gene amplification assay used in Example 170.

It is noted that at pages 7-10 of the Brief, Applicants cite pertinent case law reviewing the legal standard of utility and the Utility Examination Guidelines. The Examiner takes no issue with Applicant's general comments regarding the legal standard for utility.

At p. 11-12 and 15 of the Brief, Applicant maintains that the specification at, for example, Table 9B of Example 170, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1153 nucleic acids. Applicant argues that Example 170 discloses that PRO1153 is significantly overexpressed in several human tumor tissues as compared to a non-cancerous human tissue control. Applicant indicates that Table 9B explicitly

states that PRO1153 is significantly overexpressed in lung adenocarcinomas and squamous cell carcinomas as compared to universal normal control. Applicant argues that the utilities of PRO1153 polypeptide include the use as a diagnostic tool.

Applicants discuss the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number and that this increase is significant and useful. Applicant directs the Examiner to page 3 of the Goddard declaration that describes the gene amplification technique in the present application and references that attest to the use of this technique in diagnostic and prognostic fashion. This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1153 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1153 nucleic acid was amplified in two types of cancer samples (lung, and squamous), to a minor degree (about 2.16 to 2.85 fold) compared to blood from normal subjects. No mutation or translocation of PRO1153 has been associated with any type of cancer versus normal tissue.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (cited in the Office Action of 1 October 2004) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples

and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). It should be noted that that research group was quite cautious in their data interpretation, and yet they had used matched tissue controls, unlike the instant Application.

Applicants cite the Declaration of Dr. Goddard and argue that it is known in the art that detection of gene amplification can be used for cancer diagnostics regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. While this is true, because the proper control was not used, it is not known if the gene is amplified compared to normal *matched* tissues. Therefore, the asserted utility is not substantial, as the real-world use has not been established, because the correct control was not used. The proposed use of the anti-PRO1153 nucleic acids as claimed in this application are simply starting points for further research and investigation into potential practical uses of the gene products. There is no "overwhelming" evidence from the gene amplification data in the specification indicating that the gene encoding PRO1153 is significantly amplified in certain lung and squamous tumors. Neither the specification as filed nor the general knowledge in the art support the asserted utility as being substantial, i.e. as being anything but an invitation to further experimentation.

As discussed in the previous Office Action of 1 October 2004, the instant specification provides data showing a small increase in DNA copy number in two different types of tumor tissue (lung and squamous) (p. 517-519).

Therefore, given the small increase in DNA copy number of PRO1153 in only three tumor samples, and the fact that comparisons were not made with matched tissue, it is clear that one skilled in the art would not assume that one could detect a meaningful DNA amplification in the cancer tissue sample shown. Further research needs to be done to determine whether the increase in PRO1153 DNA is real or meaningful or indicates a role for PRO1153 in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete (*Brenner v. Manson* 1966, 383 U.S. 519, 148 USPQ 689).

The Examiner maintains that, for reasons cited above, it is more likely than not that the claimed PRO1153 nucleic acids do *not* possess the necessary diagnostic utility. The art clearly shows that such a correlation occurs for only a small minority of genes that are amplified at levels consistent with those shown for PRO1153. It is also noted that the specification of the instant application does not teach a change in DNA, especially as compared to normal tissue. The specification simply discloses a static measurement of PRO1153 DNA in squamous and lung tumor samples as compared to a blood control. Therefore, the Examiner maintains that Applicant's measurement of a purported increase in PRO1153 DNA does not provide a specific and substantial utility for the PRO1153 gene.

Applicants assert that the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. Applicants contend that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the Specification and application of an improper, heightened legal standard. Applicants state that the art indicates that, if a gene is amplified in cancer, it is more likely than not that the gene plays a role in development of that cancer in the tissue and that it may therefore be used for diagnosis (Brief, p. 6).

Applicant's arguments have been fully considered but are not found to be persuasive. The rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. Applicants do not know whether the PRO1153 gene was amplified in the lung tumor samples and colon tumor sample. Since proper controls were not utilized, any purported differences between tumor tissue and blood could easily be due to the differences inherent in the tissue themselves, and not due differences in gene expression that occurs during a cancerous state.

Applicants also discuss the Goddard Declaration as testimony from an expert in the field that the data are significant (Brief, p. 11). Applicants' arguments and the Goddard declaration have been fully considered but are not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry

Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). There is no specific indication in the Goddard declaration that the PRO1153 gene was amplified relative to normal matched tissue. Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Goddard is employed by the assignee. Finally, Dr. Goddard refers to facts; however, the data is not included in the Declaration so that the examiner could independently evaluate them.

In the instant case, the PRO1153 polypeptide and claimed nucleic acids are not disclosed as having a specific activity or having any property that can be specifically useful. The claimed invention is, in fact, the object of further study, merely inviting further research. Moreover, use of the PRO1153 polynucleotide for screening purposes is only useful in the sense that the information that is gained from the screen is dependent on the gene amplification relative to normal lung or colon tissue. Given this consideration, the claimed PRO1153 polynucleotides have no "well-established" use.

While it is agreed that the disclosure of an additional human polynucleotide (PRO1153) provides more information in regard to the human genome, in the absence of any additional information in regard to any property other than its sequence, the isolation of the PRO1153 polynucleotide of the instant application is only useful as a starting point for researchers to further investigate its biological significance, and therefore the utility of the claimed PRO1153 nucleic acids as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility.

It remains that for the PRO1153 gene, a 2.04 to 2.87 fold amplification of the genomic DNA has not been definitively established for the two types of tumors. The Examiner maintains

that the data in the specification would not be considered by one skilled in the art to be reasonably predictive that the claimed nucleic acids have diagnostic, prognostic or therapeutic utility.

In conclusion, it is noted that M.P.E.P. § 2107(I) states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO1153 polynucleotides are useful as diagnostic markers for cancer or as therapeutic targets for cancer drugs is not substantial in that further research is required to reasonably confirm a real world context of use. In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the claimed nucleic acids, and would have had to experiment further to reasonably confirm whether or not claimed PRO1153 nucleic acids can be used as a cancer diagnostic agent.

Claims 124, 129-131 and 135-145 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant's arguments (14 November 2005 and 30 June 2006), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant states that a substantial and asserted utility has been disclosed above for the polypeptide of PRO1153 and the claimed nucleic acids. Applicant's arguments have been fully

considered but are not found to be persuasive. Specifically, since Applicants have not provided evidence to demonstrate that the PRO1153 polynucleotide has a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the PRO1153 polynucleotides, polypeptides and antibodies.

Conclusion

No claims are allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
26 September 2006

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